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10/562,086	12/23/2005	Peter J. Quesenberry	59441(11259)	3235

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EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
AFREMOVA, VERA	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,086	QUESENBERRY, PETER J.	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *14-28 and 32-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-13 and 29-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/24/2008;12/16/2008*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-28 as amended and newly added claims 29-53 (9/24/2008) are pending.

Claims 14-28 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on 12/07/2007.

Original claims 1-13 were elected and examined in the prior office action.

Newly submitted claims 32-53 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The claimed inventions do not relate to a single general inventive concept under PCT Rule 13.1 because this application contains claims drawn to more than one of permissible combinations of categories of inventions such as more than one product, more than one process of use said product and more than one process specially adapted for the manufacture of said product. Newly submitted claims 32-53 are directed to third method of making product (claims 32-41) and to fourth method of making product (claims 42-53). Furthermore, as it was explained in the prior office action (10/26/2007) the corresponding special technical feature such as production of bone marrow-derived hematopoietic cells as intended for treating cytopenia are known in the art. For example: see US 6,495,365 (col. 1, lines 40-43, 51-55 and col. 3, lines 46). Thus, unity of inventions is lacking. See MPEP 1850. 37 CFR 1.475.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 26-53 have withdrawn from consideration as being directed to non-elected invention(s). See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1-13 as amended and new claims 29-31 are under examination in the instant office action.

Claim Rejections - 35 USC § 112

New claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is rendered indefinite by recitation about of "a reversible differentiation hotspot" for stem cells. It is uncertain into what cell type the stem cells would de-differentiate or reverse.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 7-9, 12 and 13 as amended and new claims 29-31 remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Hagihara et al. (IDS reference).

Claims are directed to a method for the production of differentiated hematopoietic cells wherein the method comprises 1) step of culturing purified bone marrow stem cells under conditions that promote synchronous progression through the cell cycle, 2) step of contacting the cells with a growth factor or a cytokine at predetermined phase of the cell cycle and 3) step of subculturing the cells until differentiated hematopoietic cells are produced. Some claims are further drawn to contacting and subculturing cells with the growth factor such as GM-CSF.

Some clams are further drawn to culturing cells under conditions that promote synchronous progression through the cell cycle such as culturing in the presence of steel factor, thrombopoietin and FLT-3 ligand. Some claims are further drawn to subculturing cells for about 14 days. Some claims are further drawn to additional step of isolating the differentiated hematopoietic cells from the subculture. Some claims are further drawn to the differentiated hematopoietic cells "comprising" megakaryocytes, granulocytes and platelets. Some claims are further drawn to the predetermined phase of the cell cycle being "hotspot" that "favors" differentiation or specific differentiation.

Hagihara et al. disclose a method for the production of differentiated hematopoietic cells including dendritic cells wherein the method comprises 1) step of culturing purified CD34+ bone marrow stem cells "under conditions that promote synchronous progression through the cell" that are contacting and culturing the cells with a medium comprising steel factor, thrombopoietin and FLT-3 ligand; 2) subsequent step of contacting the cells with growth factor GM-CSF at a "predetermined" phase or time of cell cycle; and 3) subculturing the cells with a growth factor GM-CSF for up to 14 days or about 14 days. (entire document including abstract and page 49 at section 2.4 "Culture system"). The method taught by Hagihara et al. comprises identical active steps and it results in the production of the differentiated hematopoietic cells as required by the claimed method and, thus, the cited reference by Hagihara et al. clearly anticipates claimed invention of the instant claims 1-4 and 13. Although production or generation of dendritic cells is a primary goal of the cited reference by Hagihara et al., the dendritic cells were not the sole cellular product of the disclosed culturing method and, thus, the final subculture after subculturing with maturation factors including GM-CSF and/or steel factor is reasonably

expected to "comprise" at least some amounts of megakaryocytes, granulocytes and platelets within the broadest reasonable meaning of the claims 7-9 and 12.

With respect to newly added claims 29-31 it is noted that the cited method of Hagihara et al results in the production of differentiated hematopoietic cells, and, thus, the step (b) of contacting the cells with a factor inherently takes place at the moment of "hotspot" that "favors" differentiation or specific differentiation within generic meaning of the claims.

Therefore, the cited reference by Hagihara et al. is considered to anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13 as amended and new claims 29-31 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Hagihara et al. (IDS reference) taken with Feng Yan et al. (Blood, November 2000, Vol. 96, No. 11, part 1, 680a), Klabusay et al. (Blood, November 2002, Vol. 100, No. 11, Abstract No. 4118), Ramsfjell et al. (Blood, December 1996, Vol. 88, No. 12, pages 4481-4492) and Messner et al. (Blood, November 1987, Vol. 70, No. 5, pages 1425-1432).

Claims are directed to a method for the production of differentiated hematopoietic cells wherein the method comprises 1) step of culturing purified bone marrow stem cells under conditions that promote synchronous progression through the cell cycle, 2) step of contacting the cells with a growth factor or a cytokine at predetermined phase of the cell cycle and 3) step of

subculturing the cells until differentiated hematopoietic cells are produced. Some clams are further drawn to culturing cells under conditions that promote synchronous progression through the cell cycle such as culturing in the presence of steel factor, thrombopoietin and FLT-3 ligand. Some claims are further drawn to contacting and subculturing cells with the growth factor such as GM-CSF. Some claims are further drawn to subculturing cells for about 14 days. Some claims are further drawn to additional step of isolating the differentiated hematopoietic cells from the subculture. Some claims are further drawn to the differentiated hematopoietic cells "comprising" megakaryocytes, granulocytes and platelets. Some claims are further drawn to the predetermined phase of the cell cycle being mid-S phase or late S phase.

The reference by Hagihara et al. is relied upon as explained above for the disclosure of a method for the production of differentiated hematopoietic cells from bone marrow hematopoietic stem cells by changing the cytokine cocktail combination of steel factor (SCF), thrombopoietin (TPO) and FLT-3 ligand (FLT3) to other factors including GM-CSF.

The cited reference by Hagihara et al does not explicitly recite that the culturing of cells in the presence of steel factor (SCF), thrombopoietin (TPO) and FLT-3 ligand (FLT3) promotes synchronous progression of the cells through the cell cycle. However, the reference by Yan et al. clearly teaches that the combination of factors SCF, TPO and FLT-3 in the culture medium stimulates the hematopoietic bone marrow cells to enter into synchronous cell cycle from resting state. For example: see abstract, wherein Yan et al. clearly disclose that the purified bone marrow cells were quiescent (non-diving or "resting" at G0/G1 phase) at the beginning of the culture, that the addition of cytokines SCF, TPO and FLT-3 stimulated the cells to enter into the cycle and that the amount of synchronous cells in S phase increased during culturing in the presence of

cytokines SCF, TPO and FLT-3.

The cited reference by Hagihara et al. clearly teaches incorporation of factor GM-CSF in the culture medium for differentiation of hematopoietic bone marrow stem cells but the reference is lacking particular disclosure about the use of G-CSF. However, the reference by Klabusay et al. teaches that hematopoietic stem cells are able to regenerate hematopoiesis in all lineages and that addition of G-SSF in particular will significantly increase the number of maturated cells including granulocytes (see abstract). The reference by Ramsfjell et al. teaches that the use of factor SCF enhances megakaryocyte differentiation and production from stem cells.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify method of Hagihara et al. by adding G-CSF and steel factor (SCF) during subsequent culturing/subculturing steps with a reasonable expectation of success in producing differentiated hematopoietic cells including megakaryocytes and granulocytes because the prior art teaches and suggests the use of G-CSF and SCF for enhancing production of granulocytes and megakaryocytes. It is well known that platelets are products of megakaryocytes. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

Further, the reference by Messner et al. teaches that cell cycle studies and stem cell engraftment studies indicate that the higher than normal proportions of multipotential hematopoietic cells are present in S phase during progression of the hematopoietic cells through the cell cycles (see abstract). Thus, one of skill in the art would have been motivated to contact the hematopoietic stem cells with maturation factors at the time of cell progression through S-phase for the expected benefits in maximizing yields of matured differentiated hematopoietic

cells derived from the stem cells. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 9/24/2008 have been fully considered but they are not persuasive.

With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by Hagihara et al. Applicant argues (response page 14) that the cited reference does not explicitly acknowledge that the use of factors SCF, TPO and FLT-3 ligand provides for "conditions that promote synchronous progression through the cell cycle". Nevertheless, the reference clearly recites the addition of factors SCF, TPO and FLT-3 ligand for culturing purified bone marrow stem cells and, thus, the cited method comprises identical conditions within the meaning of the instant claims. The cited method further comprises transfer of the cells every week into another medium with another cytokine mixtures comprising GM-CSF and thus, the cited method comprises steps of "contacting the cells with at least one grown factor at the predetermined phase of the cycle" within the broadest reasonable meaning of the claims. Applicants further argue (page 15, par. 1) that the term "every week" is not the time for "predetermined phase of the cycle". Yet, the claims are not limited by time.

With regard to the claim rejection under 35 U.S.C. 103 Applicant argues (response page 1t) that the cited references by Yan, Klabusay, Ramstjell, and Messner, taken either alone or in combination together, fail to supply the deficiencies of Hagihara.

This argument is not found particularly persuasive because the teaching of Yan et al. clearly demonstrates the inherency of events and effects in the cited method of Hagihara et al. Although Hagihara et al do not explicitly recite that the culturing of cells in the presence of steel factor (SCF), thrombopoietin (TPO) and FLT-3 ligand (FLT3) promotes synchronous progression of the cells through the cell cycle, the reference by Yan et al. teaches that the combination of factors SCF, TPO and FLT-3 in the culture medium stimulates the hematopoietic bone marrow cells to enter into synchronous cell cycle or into S phase from resting state (G0 phase) after 24 hours of initiation of the culture.

Applicant appears to argue that the combination of the cited references would not suggest a transfer of synchronous cells into a differentiation medium at a "predetermined phase of the cycle" for production of differentiated cells. Yet, the claim 1 is not limited by specific time and by specific differentiation medium or factors as intended. Although claims 6 and 11 are limited by time of contacting cells with factors, these claims are drawn to the use of some generic factors. Thus, the combination of Hagihara et al. and Yan et al. teaches and suggests the presently claimed method because in the method of Hagihara et al the culture of synchronously diving cells (in view of Yan et al.) is contacted through the whole culture period (including 32 and 40 hours after initiation) with the same factors as claimed. The method of Hagihara et al. results in the production of a mixture of differentiated cells including DC cells, for example. The references by Klabusay et al. and Ramsfjell et al teach and suggest that the use of specific factors

as claimed such as G-CSF and steel factors would promote production of differentiated cells such as granulocytes and megakaryocytes from stem cells. Thus, combination of the cited references would teach and suggest one of skill in the art the presently claimed invention.

With respect to Messner applicant argues that this work is irrelevant to the present invention. This argument is not found particularly convincing because this reference teaches S-phase as "hot spot" for initiation of cell differentiation since proportion of multipotential hematopoietic cells in higher in S phase during progression of the hematopoietic cells through the cell cycles (see abstract). Thus, one of skill in the art would have been motivated to contact the hematopoietic stem cells with maturation factors at the time of cell progression through S-phase for the expected benefits in maximizing yields of matured differentiated hematopoietic cells derived from the stem cells.

Therefore, the claims are properly rejected under 35 USC § 103

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1657

January 16, 2009

VERA AFREMOVA

PRIMARY EXAMINER

/Vera Afremova/
Primary Examiner, Art Unit 1657